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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,693	BERLIN ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, Claims 1-14 in the reply filed on 1/08/2007 is acknowledged. The traversal is on the ground(s) that Claim 15 drawn to a kit now comprises method limitations. This has been thoroughly reviewed but has not been found persuasive. This is not found persuasive because under 371 the claims have not been shown to share a special technical feature over the art because as indicated in the requirement for restriction (p. 3 mailed 11/30/2006) the art teaches the technical feature of the claims and the groups do not show a special technical feature over the art. The amendments to the claims are not sufficient to remove the restriction because on the lack of a special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-15 are pending. Claim 15 is withdrawn as drawn to a nonelected invention.

3. An action on the merits for Claims 1-14 is presented below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 3 and 10-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is identified over the phrase "conditioned". This term is not defined in the specification and is not an art recognized term used to describe how one treats a biological sample.

Claims 10-11 are indefinite over the phrase "abnormal level of free floating DNA". It is unclear what level of free floating DNA is considered abnormal and therefore the metes and bounds of the claim are unclear.

Claim 11 is indefinite. It is unclear if the "free floating DNA" in step c is the same as the "total free floating DNA" in step b.

Claims 12-14 recites the limitation "the total free floating DNA" in step c of Claim 12. There is insufficient antecedent basis for this limitation in the claim. It is unclear if the total free floating DNA is the same as the free floating DNA present in the preamble.

Claims 12-14 are unclear over the phrase "determining the fraction of total free floating DNA". It is unclear because there is no process step of comparing the quantity of total free floating DNA to another quantity of DNA to determine a fraction. It is unclear how the method steps of amplifying and analyzing the treated DNA allow for the determination of the fraction of total free floating DNA.

Claims 13-14 are indefinite over the phrase "abnormal level of free floating DNA". It is unclear what level of free floating DNA is considered abnormal and therefore the metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While the art does enable one of skill in the art to analyze cytosine methylation in free floating DNA neither the art nor the specification enables one of skill in the art to determine the presence or absence of ANY diseased condition in a tissue, cell type or organ. Further neither the specification nor the art enables one of skill in the art to detect the presence or absence of a diseased condition by determining the amount or presence of free floating DNA without any methylation step.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Breadth of the claims

Claim 1 is drawn to obtaining a sample, determining an amount or presence of free floating DNA and determining the presence or absence of a diseased condition based on the amount or presence of free floating DNA. Claim 2 is drawn to a method comprising obtaining fluid, determining an amount of total free floating DNA and an amount which originates from a particular tissue, cell type or organ and determining the presence or absence of a diseased condition based on the total amount and the fraction. Claims 3-4 define the conditions. Claims 5-6 comprises a step of determining methylation pattern. Claim 7 defines the diseased condition. Claim 8 defines the sample. Claim 9 comprises a step of determining methylation pattern. Claim 10 is drawn to a method comprising determining abnormal level of free floating DNA to determine the presence or absence of a diseased condition. Claim 11 adds a methylation limitation step. Claim 12-13 comprises a method to determining diseased condition by detecting methylation of bound DNA. Claim 14 defines the measuring assay.

The claims encompass methods of merely detecting free floating DNA, wherein the specification is drawn to methylation steps. The claims encompass detection of ANY disease state, which includes not only neoplastic diseases but also diseases such as Alzheimer's', depression, and hypertension. The specification does not provide specific working examples for the broad claim language. The claims encompass detection of free floating DNA whereas the art teaches that it is unpredictable to

associate free floating DNA with disease.

The claims are broadly drawn to any individual. Any individual would include any species such as human, chipmunk, and peacock. The art teaches that the correlation of mutations with disease or disorder is species dependent and therefore associations in one species such as human cannot be extrapolated to ANY subject.

When the claims are read in light of the specification, the specification discloses a methodology to detect mutations but does not provide any correlative associations for the detection of any disease. Further the specification does not disclose correlative associations with detection of disease without any methylation steps.

Nature of the Invention

The claims are broadly drawn to a method of determining the presence or absence of a diseased condition that originates from the tissue, cell type or organ. The claims broadly encompass ANY diseased condition that originates from ANY tissue, cell type or organ. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Teachings in the Specification and state of the art

The specification asserts a means to predict which organ, tissue, or cell type has developed a medical condition, by employing means of distinguishing between DNA originating from different healthy or different diseased tissues, organs or cell types of

the human body (p. 19 last paragraph). The specification asserts characteristic methylation patterns of certain genes can be positively correlated with specific organs, tissues, and cell types (p. 19 last paragraph). However, the specification does not disclose an association in any individual, such as dog, cat, or peacock only human.

Further the specification does not provide a predicative association of the detection of any disease by the detection methylation patterns. It is unpredictable that any disease would be detectable in free floating DNA because it is unclear if any tumor, organ, or tissue can be detecting in a fluid sample. Therefore the skilled artisan would have to perform undue experimentation in order to determine the method steps needed to detect any tumor, organ, or tissue in a fluid sample and use this detection to determine disease status.

The specification asserts the knowledge achieved allows to predict if the individual carries a medical condition, such as a cell proliferative disease in said tissue, organ or cell type (p. 22 5th paragraph). The specification asserts a patient with a substantial amount of free floating DNA originating from liver, might have developed a liver tumor (p. 22 5th paragraph). The specification asserts that to validate this, the next step could be to employ, for example, a tailored test assay for disease indicating marker gene expression, specific for said organ or tissue (p. 22 5th paragraph). Therefore the specification asserts that validation studies must be performed in order to clearly associate detection of free floating DNA with detection disease.

The specification asserts that methylation patterns found in the tested sample will be identified as belonging to a certain tissue, cell type or organ (p. 34 5th paragraph).

The specification asserts that methylation patterns can be associated either by comparing the individual data set resulting from said analysis to data received in previous studies or to a dataset obtained in a parallel experiment on one or preferably more control fluids (p. 34 last paragraph). The specification indicates that to determine if methylation patterns are associated with disease a comparison study must be done, however, the claims as broadly written, merely comprise the detection of methylation patterns.

Post filing art, Cottrell (clinical Biochemistry 2004 Vol. 37 p. 595) teaches that because methylation-based markers are not routinely used in clinical labs, the methodology has not been fully optimized, validated, and standardized. Cottrell et al. teaches that most of the methylation methods rely on bisulfite treatment protocol which must meet strict requirements for consistency and performance (p. 601 1st column 2nd full paragraph). Cottrell et al. teaches that in order to discover optimal markers and crease successful assays, there will need to be clearly defined clinical questions, sample sets, and methodologies coupled with the current methylation technologies (p. 601 1st column last paragraph).

Based on the data presented in the specification and the teachings in the art, it is unpredictable to correlate the methylation pattern of any free floating DNA to ANY disease condition by detecting methylation patterns (or merely detecting DNA). The art teaches the lack of predictability with regard to methylation pattern studies and correlation to any disease condition.

Figure 7 is disclosed in the specification as the result of the study wherein DNA

methylation pattern of specific CpGs in DNA from four different tissues has been analyzed (p. 42). The specification discloses that methylation analysis from CpG positions correlate to the specific tissue types (p. 43). However, the art teaches that using circulating DNA as a diagnostic tool is unpredictable and that methylation patterns are not reproducible.

Ziegler et al. reviewed literature related to the diagnostic potential of circulating DNA (Cancer Treatment Reviews, 2002 Vol. 28, pp. 255). Ziegler et al. state that fraction of plasma DNA contributed by tumors varies from 3-93%, undermining their utility as diagnostic tool (p 256, last paragraph). Ziegler et al. stress the need for standardization and selection of patients for the studies (p 257, 2nd paragraph). Ziegler et al. also teach that the studies performed to date show variable levels of correlation between circulating DNA levels and cancer (Table I; page 257, last paragraph; page 259, first and second paragraphs). Ziegler et al. also reviewed references related to the determination of gene hypermethylation in circulating DNA of patients with cancer. They teach that even though some genes like APC, methylation of which is present in 96% of lung cancers, enable prediction of patient survival, methylation of other genes was shown to be not significantly associated with the presence of cancer in patients with non-small cell lung cancer (NSCLC) (p 261, last paragraph), and contradictory results were obtained for other cancers as well (p 262).

In summary, the claims encompass the detection of any disease using samples from any individual by the detection of free floating DNA or the detection of methylation patterns of free floating DNA, however, the specification does not provide guidance as

to how to make associations between any disease in any individual by the detection of free floating DNA. Moreover, the specification indicates that the correlation of disease and free floating DNA must have an association step to compare to a normal individual and a validation study. The associations are unpredictable, because the specification provides no statistically significant association between any disease and detection of free floating DNA, further the art teaches that theses associations are unpredictable.

The predictability or unpredictability of the art and degree of experimentation

The art teaches genetic variations and associations are often irreproducible and that there are many parameters that need to be evaluated prior to using a genetic test to determine a disease. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

The art teaches that there is unpredictability in associating circulating DNA (free

floating) with disease. The post-filing art, Bremnes et al. (Lang Cancer 2005 Vol 49 p. 1) teaches a review of circulating DNA in lung cancer by evaluating the role of circulating DNA in 22 studies (abstract). Bremnes et al. teaches the analysis of circulating DNA in plasma might lead to increasing clinical impact, however, large perspective clinical studies are needed to validate and standardize any test for DNA alteration in plasma or serum of high risk individuals or patients with established lung cancer (Abstract). Therefore there is still unpredictability with correlating circulating DNA in plasma and serum with disease condition.

Jung et al. (Cancer Letters 2004 Vol 205 p. 173) teaches the presence of circulating DNA (free floating) in patients with prostate cancer and benign prostate hyperplasia (BPH) (abstract, page 174-175 1st two paragraphs). Juang et al. teaches that patients with metastases had higher levels of circulating DNA, the DNA levels in cancer patients without metastases were not significantly different from the normal controls, whereas some of the BPH patients had circulating DNA levels higher than normal (p. 175-176 and Figure 2). Jung et al. teaches that plasma DNA (free floating) has a limited validity as metastatic marker in prostate cancer patients (Abstract).

As evidenced by current literature, circulating DNA is not always correlated with the presence of cancer in a subject. Sidransky et al. (Ann. NY Acad. Sci.,2000 vol. 906, pp. 1), the origin of circulating DNA in the blood is uncertain (page 3, second paragraph), and "these studies raise significant issues about the biology and physiology of how the DNA is released and maintained in the circulation and ultimately on its clinical value" (page 3, third paragraph). Sindransky states further "However, it is

abundantly clear that large prospective studies with longitudinal follow up are essential if we are to carefully evaluate these circulating DNA markers and eventually integrate them into the clinical setting."

The current art teaches that methylation is not only caused by neoplasms, but that methylation can be detected in normal tissue. This indicates that detection of methylation does not indicate neoplasic tissue. The current art teaches detection of methylation is indicative of not only neoplasm but also aging of normal cells. Yates et al. (Oncogene 2006 Vol 25 p. 1984) teaches that methylation increases with age and malignancy (abstract). Yates et al. teaches that methylation was detected in urine DNA from patients with and without bladder cancer (Abstract). Yates et al. teaches aberrant methylation is not cancer specific and can be found in a normal ageing cell population (p. 1985 1st column 1st paragraph). Yates et al. teaches the overall knowledge of the molecular mechanisms of DNA methylation in health and cancer remains poor and one uncertainty is the extent of aberrant DNA methylation in nonmalignant tissue and the association between ageing and aberrant DNA methylation (p. 1985 last paragraph).

Amount of Direction or Guidance Provided by the Specification

The specification does not provide any specific guidance as to how to correlate detection of any disease by the detection of free floating DNA. The specification discloses that a correlation to disease must include an association step to compare methylation patterns to individuals and a validation study to confirm detection of disease.

The art teaches detection of disease with methylation patterns in free floating DNA is

unpredictable and that these associations need to be confirmed by multiple large sampling sizes to determine a clear association. The skilled artisan, therefore, would have to perform undue experimentation to determine the correlation of disease detection to detection of free floating DNA as it is broadly written in the claims.

Working Examples

The specification provides no examples to correlate detection of disease by detection of free floating DNA in any individual. Example 1 describes determining plasma blood from one patient to detect neoplastic disease (p. 43). The specification asserts that it was concluded a significant portion of the DNA in the patient's blood derived from his lung, the physician now referred the patient to a hospital that is specialized on inflammatory or cell proliferative diseases of the lung. However, the specification does not provide any pvalue, therefore, it is unclear how to extrapolate the example of one specific patient to the detection of a large portion of DNA derived from lung to the detection of any disease by detection of free floating DNA.

The specification asserts three more patient samples with detection of serum DNA levels (p 43-44), however there are no working examples showing an statistically significant association of any disease. The first three experiments only had an association of a specific patient and a specific disease, whereas it is unclear the number of patients in the 4^{th} experiment.

Furthermore, the specification provides no indication as to whether the detection of a methylation pattern is significant such that the skilled artisan would be able to predictably correlate the results which any disease condition. The specification does not have an example of determining in ANY sample a correlation of methylation pattern with detection or ANY diseased condition.

Therefore, though the specification provides a few studies of the correlation of one patient and the detection of one tissue type and as presented in figure 7 the correlation of specific CpG island methylation patterns and tissue type, the art as discussed above teach that these associations are unpredictable. The art teaches that the correlation of methylation patterns to any disease in any given population is not reproducible. The skilled artisan, therefore, would have to perform undue experimentation in order to determine if methylation patterns in circulating DNA is correlative to any disease.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters, which would have to be studied prior to being able to practice the claimed invention as broadly as written. The skilled artisan would have to determine the association of any detection of disease with measurement of free floating DNA. The skilled artisan would then have to determine if this association was species base. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed

invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification does not provide any predictable association of detection of free floating DNA and any disease. Further the art teaches that the measurement of free floating DNA and associations made are unpredictable. In view of this unpredictability, the specification has not established that the presently claimed method can be used to determine the detection of any disease by the detection of free floating DNA or methylation patterns of free floating DNA>

Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-8, 10-11, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Goessl et al. (Cancer Research 2000 Vol. 60 p. 5941).

With regard to Claim 1, Goessl et al. teaches obtaining plasma, serum, ejaculate and urine from patients (abstract and p. 5941 Patients and Methods DNA Isolation). Goessl et al. teaches determining the presence of GSTP1 (DNA from prostate tumor tissue) (Abstract). Goessl et al. teaches determining the presence of prostate cancer (a disease) based on the presence of GSTP1 in bodily fluids (Abstract).

Claim 2 is identical in scope to Claim 1 except that Claim 2 has a further limitation of determining the amount of total free floating DNA and the amount of free floating DNA that originates from a particular tissue, cell type, or organ. With regard to Claim 2, Goessl et al. teaches a methylation specific PCR technique (MSP)which detects 200 prostate cancer cells (free floating DNA originating from a tissue type) in 2.2 X 10^7 nonmalignant leukocytes (total DNA) in a blood sample (p. 5942 second column 1st full paragraph).

With regard to Claims 3-4, Goessl et al. teaches that the free floating DNA was modified by bisulfite treatment (chemical treatment) before detection of the amount or presence of DNA was determined (p. 5941 last paragraph).

With regard to Claim 5, Goessl et al. teaches detection of a methylation pattern to determine the presence of DNA from prostate tissue (abstract).

With regard to Claim 6, Goessl et al. teaches the MSP technique to determine methylation patterns unique to the GSTP1 gene to determine that this gene is in the bodily fluids (abstract and p. 5941-5942 Fluorescent MSP).

With regard to claim 7, Goessl et al. teaches detection of prostate cancer (neoplastic disease) (abstract).

With regard to Claim 8, Goessl et al. teaches plasma, serum, ejaculate, and urine fluids (Abstract).

With regard to Claims 10-11, Goessl et al. teaches obtaining plasma, serum, ejaculate and urine from patients (abstract and p. 5941 Patients and Methods DNA Isolation). Goessl et al. teaches determining the presence of GSTP1 (DNA from prostate tumor tissue) (Abstract). Goessl et al. teaches the MSP technique to determine methylation patterns unique to the GSTP1 gene to determine that this gene is in the bodily fluids (abstract and p. 5941-5942 Fluorescent MSP). Goessl et al. teaches that prostate cancer is detected by the detection of methylated GSTP1 alleles in fluids (e.g. an abnormal level) (Figure 3).

With regard to Claim 14, Goessel et al. teaches a PCR detection method (amplification procedure with subsequent determination of amount of product amplificate formed (p. 5941-5942 Materials and Methods).

6. Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Goessl et al. (Cancer Research 2000 Vol. 60 p. 5941) as evidenced by Rein et al. (Nucleic Acids Research 1998 Vol. 26 p. 2255).

Goessl et al. teaches obtaining plasma, serum, ejaculate and urine from patients (abstract and p. 5941 Patients and Methods DNA Isolation). Goessl et al. teaches determining the presence of GSTP1 (DNA from prostate tumor tissue) (Abstract). Goessl et al. teaches determining the presence of prostate cancer (a disease) based on the presence of GSTP1 in bodily fluids (Abstract). Goessl et al. teaches that the free floating DNA was modified by bisulfite treatment (chemical treatment, methylation) before detection of the amount or presence of DNA was determined by MSP (methylated PCR) (p. 5941 last paragraph). With regard to Claim 9, Rein et al. teaches that bisulfite treatment converts all unmethylated cytosines in the DNA into uracil but leaves position 5-methylated cytosines unmodified (Table 1 and Figure 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C: 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goessl et al. (Cancer Research 2000 Vol. 60 p. 5941) in view of Heiskanen et al. (Cancer Research 2000 Vol 60 p. 799) as evidenced by Rein et al. (Nucleic Acids Research 1998 Vol. 26 p. 2255).

With regard to Claim 12 a, Goessl et al. teaches obtaining plasma, serum, ejaculate and urine from patients (abstract and p. 5941 Patients and Methods DNA Isolation).

With regard to Claim 12 e, Goessl et al. teaches determining the presence of prostate cancer (a disease) based on the presence of GSTP1 in bodily fluids (Abstract). Goessl et al. teaches that the free floating DNA was modified by bisulfite treatment (chemical treatment, methylation) before detection of the amount or presence of DNA was determined by MSP (methylated PCR) (p. 5941 last paragraph). Rein et al. teaches that bisulfite treatment converts all unmethylated cytosines in the DNA into uracil but leaves position 5-methylated cytosines unmodified (Table 1 and Figure 2).

With regard to Claim 12 f, Goessl et al. teaches amplifying the methylated DNA (p. 5942 1st column 1st paragraph).

With regard to Claim 12 g, Goessl et al. teaches analyzing methylation specific positions in the treated DNA to determine the amount of DNA, which has a methylation pattern (Figures 1-3).

With regard to Claim 12 h, Goessl et al. teaches determining the amount of DNA from a specific tissue (Figure 3).

With regard to Claim 13, Goessl et al. teaches associating the presence of methylated DNA to prostate cancer (Abstract and Figure 3).

Goessl et al., however, does not teach (b) conditioning the sample to provide for binding of free floating DNA to a surface; (c) binding an amount of the total free floating DNA to the surface; (d) detecting an amount of total free floating DNA by measuring the amount of DNA bound to the surface.

Heiskanen et al. teaches a method of taking a target DNA and binding it to a surface (microarray) before using the target to detect expression levels (abstract).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Goessl et al. by binding the target DNA (free floating DNA) to a microarray as taught by Heiskanen et al. The ordinary artisan would be motivated to improve the method of Goessl et al. by binding the target DNA (free floating DNA) to a microarray as taught by Heiskanen et al. because Heiskanen et al. teaches that by binding the DNA to a microarray parallel analysis of genomic DNA for expression analysis allows fro a rapid approach to the identification of amplified genes in tumor cells.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon
Examiner
Art Unit 1634

CARLA J. MYERS
PRIMARY EXAMINER